Roles of Radiotherapy and Smoking in Lung Cancer Following Hodgkin's Disease

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Background: **Several studies have shown that survivors of Hodgkin's disease have increased risk of lung cancer, but the factors responsible for this excess risk are not well known.** ***Purpose:*** **This study was undertaken to investigate the effects of radiation dose, chemotherapy, and smoking on the risk of lung cancer following treatment of Hodgkin's disease.** ***Methods:*** **We conducted a case–control study in a cohort of 1939 patients treated for Hodgkin's disease from 1966 through 1986 in The Netherlands. Detailed treatment information was collected from the medical records for 30 case patients with lung cancer following Hodgkin's disease and 82 matched control subjects who had not developed lung cancer. Multiple sources were used to obtain as complete smoking histories of the study participants as possible. For each case–control set, the radiation dose received by the area of the lung where the case patient developed the tumor was estimated on the basis of radiotherapy charts and experimental simulations of treatments. The estimates of relative risk (RR) for lung cancer associated with specific exposures were obtained from logistic regression methods, and all tests of statistical significance were two-sided.** ***Results:*** **A statistically significant increase in risk of lung cancer was observed with increasing radiation dose (*P* for trend = .01) with an RR of 9.6 (95% confidence interval [CI] = 0.93-98) for patients who received 9 Gy or more compared with those who received less than 1 Gy. Patients who smoked more than 10 pack-years after the diagnosis of Hodgkin's disease had a sixfold increase in the risk of lung cancer compared with patients who smoked less than 1 pack-year (*P* = .03). Positive interaction on a multiplicative scale was observed between the carcinogenic effects of smoking and radiation. The increase in risk of lung cancer with increasing radiation dose was much greater among the patients who smoked after diagnosis of Hodgkin's disease than among those who refrained from smoking (*P* = .04). There was no increase in lung cancer risk in relation to the number of cycles of chemotherapy or the cumulative doses of the drugs mechlorethamine and procarbazine.** ***Conclusions:*** **The excess risk of lung cancer in Hodgkin's disease patients treated with radiotherapy is related to the radiation dose received by the affected area of the lung. Smokers experience a significantly greater risk attributable to radiotherapy than nonsmokers.** ***Implications:*** **Physicians in charge of patient treatment should make a special effort to dissuade Hodgkin's disease patients from smoking after receiving radiotherapy. [J Natl Cancer Inst 1995; 87:1530-7]**

Over the past decade, several studies *(1-7)* have shown that survivors of Hodgkin's disease experience increased risk of developing lung cancer. The majority of these studies showed that the lung cancer risk did not increase in the first few years of treatment but instead increased steadily throughout the follow-up. After 5 years or more of treatment, a threefold to eightfold excess risk of lung cancer was reported compared with the risk in the general population *(2,5-7)*. In several studies *(2-4,7)*, the excess risk of lung cancer was attributed to radiation treatment given for Hodgkin's disease. This is not surprising, because increased risk of lung cancer has been reported following a variety of radiation exposures, such as the atomic bomb explosions in Japan *(8,9)*, radon exposure in uranium mining *(10,11)*, and radiotherapy for benign conditions, such as ankylosing spondylitis *(12)*. The relationship between lung cancer risk and radiation dose has not been well quantified, particularly in the high-dose range that is commonly used for the treatment of malignant diseases. Furthermore, the joint effects of smoking and high-dose irradiation for malignant disease have not yet been investigated, because all previous studies of lung cancer risk after cancer treatment lacked data on smoking habits.

Two studies *(5,13)* have provided evidence that chemotherapy may also contribute to the excess risk of lung cancer in patients with Hodgkin's disease. Such an effect of chemotherapy, however, has not been found in other studies *(4,6)* with equivalent follow-up time; therefore, the possible association between chemotherapy and lung cancer risk deserves more extensive study.

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See "Notes" section following "References."

We report here on the results of a case–control study in which the characteristics of case patients with lung cancer from a large series of Hodgkin's disease patients (n = 1939) were compared with those of matched control subjects in whom lung cancer did not develop. Smoking histories that were as complete as possible were obtained for all subjects. The aim of this study was to assess the separate and combined effects of radiation dose, smoking, and chemotherapy on the development of lung cancer.

Subjects and Methods

Study Population

Our case-control study was conducted in a cohort of 1939 patients with Hodgkin's disease who were admitted to The Netherlands Cancer lnstitute in Amsterdam (n = 921) or the Dr. Daniel den Hoed Cancer Center in Rotterdam (n = 1018) from 1966 through 1986. Patients were identified through the hospital tumor registries of each institute. The methods used to assess second cancer risk in the cohort have been described extensively elsewhere *(4).* In brief, information on the recent medical status of each patient was collected directly from the medical records or, in the case of patients lost to follow-up, by mailing a questionnaire to specialists in other hospitals and to general practitioners. For 97% of the cohort, we obtained data on medical status up to at least January 1, 1989. Twenty-nine cases of lung cancer were observed in patients who had survived at least 1 year following a diagnosis of Hodgkin's disease against 7.3 cases expected (relative risk [RR] = 4.0 95% confidence interval [Cl] = 2.7-5.7) *(4).* For the case-control study, we added two recent cases that developed after the patients' follow-up for the cohort study had been completed. These cases were identified through linkage of the cohort database with the two hospital tumor registries from which the cohort had been derived. For 26 lung cancer patients, the histologic slides were reviewed by one pathologist. Five cases of lung cancer could not be reviewed because the slides were unavailable or of poor quality. Since we had very clear pathology reports supplemented by strong clinical data for all of the patients, these cases were retained in the analysis.

For each case patient with lung cancer, three matched control subjects were sought from the cohort of Hodgkin's disease patients. Control subjects had to have survived without a second cancer for at least as long as the interval between the diagnoses of Hodgkin's disease and lung cancer in the case patient. They were matched to the case patient within the given cancer center (for practical reasons), as well as on sex, date of birth (±3 years), and date of diagnosis of Hodgkin's disease (±5 years). When more than three control subjects per case patient met these requirements, we selected those subjects whose date of birth and then date of diagnosis of Hodgkin's disease were closest to those of the corresponding case patient. Three control subjects were found for each of 25 case patients, two control subjects each were found for two case patients, and three case patients were matched to only one control subject. Not a single control subject could be found for one case patient who developed lung cancer 24 years after diagnosis of Hodgkin's disease. This case patient was omitted from the analysis.

Abstraction of Medical Records

For all study subjects, the full medical records were obtained for detailed data abstraction of all treatments received. When part of the treatment had been given outside the two cancer centers, the two data abstractors were sent to peripheral hospitals to collect the relevant data. Information was collected on the characteristics of Hodgkin's disease (morphology and stage), all chemotherapy and radiotherapy given for Hodgkin's disease, and smoking habits. The details abstracted for each course or cycle of chemotherapy included the name and total dose of each drug used, the dates of administration, and whether the drug was given in combination. Regarding radiotherapy, we abstracted data on the size and location of the fields irradiated from the radiation chart. In addition, all radiation treatment charts were photocopied for later use in estimating dose to the lungs. After abstractors completed each data form, a physician in charge of study procedures and quality control compared all information abstracted with that on the respective medical record for accuracy. The detailed smoking history included information on duration, amount, and type of smoking prior to diagnosis of Hodgkin's disease; amount smoked at diagnosis of Hodgkin's disease; duration, amount, and type of smoking during the interval between Hodgkin's disease and lung cancer (or an equivalent interval for control subjects); and amount smoked at diagnosis of lung cancer (or an equivalent date for control subjects). Information on smoking was obtained not only from the medical records but also from the patient's general practitioner (by means of a mailed questionnaire). For three case patients and for about one third of the control subjects, information in the records was missing on duration of smoking after diagnosis of Hodgkin's disease and amount smoked at the point of time equivalent to the date of lung cancer diagnosis in the corresponding case subject. Therefore, in the case of incomplete smoking data, we attempted to collect information directly from the patient when he or she was still alive. This data collection was done by the physician in charge of treatment during a routine follow-up visit.

For several patients, the smoking histories obtained from various sources were slightly contradictory. In all of these cases, the most plausible smoking history was determined jointly by three of the authors (F. E. van Leeuwen, A. W. van den Belt-Dusebuot, and R. Noyon) without knowledge of the patient's case or control status. Only for one control subject all smoking data were missing and complete smoking histories were eventually available for 90% of the study population.

Radiation Treatments and Dosimetry

Of the patients who received radiotherapy in the study, all except three had treatment with mantle, supraclavicular, inverted-Y, splenic, or para-aortic fields, which are the fields that give the highest dose to the lung. With regard to radiation energy, 82 (73%) individuals of the study group (case patients = 30 and control subjects = 82) were treated with high-energy photons from a linear accelerator, mostly 8 MV, and the remainder of the patients were treated with either orthovoltage x rays, cobalt 60, or electrons.

On the basis of the details of radiotherapy abstracted from the radiation charts and experimental measurements, absorbed radiation doses to the five lobes of the lungs, bronchi, and trachea were estimated for each patient. The estimation of lung dose took into account radiation dose received from all radiotherapy fields, not just the mantle field. Blocking of the lungs was considered in the estimate of doses from mantle field treatments.

In the treatment simulations, absorbed dose was measured with lithium-fluoride dosimeters placed in a three-dimensional matrix in a water phantom. Simulations were repeated for different combinations of field site and size and beam energy. This measurement system is accurate to within 5%. These measured data were then used in a three-dimensional computer representation of an average-sized patient to estimate absorbed dose to any location within a patient. In the mathematical phantom, the lungs, bronchi, and trachea contained a total of 450 points of dose estimation. The points were evenly spaced in a three-dimensional grid to provide equal weight for the dose to each point when calculating average dose over a lung region. The doses reported for each patient were based on the doses calculated in the mathematical phantom and were renormalized to be consistent with the given doses stated in the patient's treatment record.

Statistical Analysis

The RR of lung cancer associated with specific exposures (e.g., treatment and smoking) was estimated by comparing the history of each case patient with that of their matched control subjects, using conditional logistic regression methods *(14).* With the microcomputer program EGRET, we calculated RR estimates (odds ratios), *P* values, and 95% Cls for the RR estimates *(15).* All tests of statistical significance were two-sided, The comparisons between exposure categories were based on likelihood-ratio tests. Because all subjects had received radiotherapy, chemotherapy, or a combination of both, it was not possible to estimate the RR of specific treatments as compared with a reference category of subjects who had never been exposed to possible carcinogenic agents. Therefore, in our analysis of the relation between lung cancer risk and radiotherapy, the comparisons were made relative to patients treated with chemotherapy alone. For case patients, we considered the therapies only in the period between the diagnoses of Hodgkin's disease and lung cancer; for each control subject, the analysis took into account only therapy abstracted in a period of equal length, starting with the diagnosis of Hodgkin's disease. There were no patients who had received radiotherapy or chemotherapy prior to the diagnosis of Hodgkin's disease.

In evaluating the association between lung cancer risk and radiotherapy for each case–control set, we used the radiation dose to the area of the lung where the lung tumor had developed in the case patient. In two lung cancer patients, the tumor site overlapped two lung areas; for both these patients (and their matched control subjects), the mean radiation dose to the affected areas was used in the analysis. The risk of lung cancer was estimated with radiation dose treated as a continuous variable or grouped into evenly spaced exposure categories.

For four subjects (4% of the study population), the dose information for one or more cycles of chemotherapy was unavailable from the medical record. For two patients, the doses could be estimated on the basis of doses given to the same patient in similar cycles; for the two other patients, the dose was estimated on the basis of the dose given to other patients treated with similar cycles. The relation between lung cancer risk and the dose of individual cytostatic agents was evaluated by grouping the cumulative dose into two exposure categories on the basis of the median dose level in the study population and computing RRs between each category and the reference group of patients who had not been treated with the drug. Tests for linear trend in the RR of lung cancer by cumulative dose of specific agents were calculated by fitting the actual milligram amounts of use as a continuous variable in the logistic regression analyses.

The relation between lung cancer risk and smoking was assessed by calculating the number of pack-years smoked before and after diagnosis of Hodgkin's disease. The number of pack-years smoked by cigar smokers was divided by 10 to yield cigarette-equivalent pack-years. For patients with incomplete smoking histories (n = 10), the number of pack-years smoked before diagnosis of Hodgkin's disease was estimated on the basis of the median number of pack-years smoked before the diagnosis of Hodgkin's disease by subjects with otherwise similar smoking behavior (as represented by smoking status and type of smoking at Hodgkin's disease diagnosis).

The interaction between smoking and radiation dose was examined in various models, with radiation dose and smoking being treated either as continuous or as categorical variables. When more than two radiation exposure categories were used, the number of subjects was so small that the conditions for convergence of the conditional logistic model were not met. For only this special case, the RRs were computed with an unmatched logistic model, with adjustment for all matching variables.

Results

Table 1 presents general characteristics of the study group. Only one (3%) lung cancer case of 30 occurred among the females who constituted 41% of the cohort (795 subjects out of 1939) from which the cases were identified. The average age at diagnosis of Hodgkin's disease was 49.9 years for the lung cancer case subjects and 49.2 years for their matched control subjects. Overall, 83% of the control subjects were matched within 2 years of the case patient's age at diagnosis of Hodgkin's disease. Of the control subjects, 48 (59%) of 82 were matched within two calendar years of the case patient's year of diagnosis of Hodgkin's disease, and 80% were matched within three calendar years. The median interval between the diagnosis of Hodgkin's disease and lung cancer was 9.2 years. The majority of lung cancers were squamous cell carcinomas. Lung cancers occurred much more often in the right lung than in the left lung (63% versus 38%), and there was a preponderance of tumors in the right upper lobe.

All but one of the lung cancer case subjects (97%) had received radiotherapy for Hodgkin's disease, as compared with 88% of the control subjects (Table 2). The overall RR of lung cancer associated with any radiation treatment was 4.1 (95% CI = 0.48-36) compared with chemotherapy alone (*P* = .19). The RR of lung cancer for patients treated with both chemotherapy and radiotherapy was slightly lower than the RR associated with radiotherapy alone, but the difference was not statistically significant (*P* = .42).

Table 1. Characteristics of case patients with lung cancer following Hodgkin's disease and their matched control subjects

Characteristic	No. of case patients (%) (n = 30)	No. of control subjects (%)* (n = 82)
Institute		
The Netherlands Cancer Institute	18 (60.0)	47 (57.3)
Dr. Daniel den Hoed Cancer Center	12 (40.0)	35 (42.7)
Sex		
Male	29 (96.7)	79 (96.3)
Female	1 (3.3)	3 (3.7)
Calendar year of diagnosis of Hodgkin's disease		
<1971	8 (26.7)	21 (25.6)
1971-1973	8 (26.7)	21 (25.6)
1974-1977	5 (16.7)	20 (24.4)
≥1978	9 (30.0)	20 (24.4)
Age at diagnosis of Hodgkin's disease, y		
<45	7 (23.3)	21 (25.6)
45-49	7 (23.3)	21 (25.6)
50-54	8 (26.7)	17 (20.7)
≥55	8 (26.7)	23 (28.0)
Stage of Hodgkin's disease†		
I	12 (40.0)	28 (34.1)
II	10 (33.3)	35 (42.7)
III and IV	6 (20.0)	18 (22.0)
Unknown	2 (6.7)	1 (1.2)
Interval between diagnosis of Hodgkin's disease and lung cancer, y		
1-4	8 (26.7)	N/A
5-9	11 (36.7)	N/A
≥10	11 (36.7)	N/A
Morphology of lung cancer		
Large-cell carcinoma	2 (6.7)	N/A
Small-cell carcinoma	4 (13.3)	N/A
Squamous cell carcinoma	18 (60.0)	N/A
Adenocarcinoma	6 (20.0)	N/A
Location of tumor within the lung‡		
Right upper lobe	14 (43.8)	N/A
Right middle lobe	0 (0)	N/A
Right lower lobe	4 (12.5)	N/A
Right bronchus	2 (6.3)	N/A
Left upper lobe	7 (21.9)	N/A
Left lower lobe	3 (9.4)	N/A
Left bronchus	2 (6.3)	N/A

*N/A = not applicable.

†Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860-1.

‡Total adds to more than 30 because two tumors overlapped two lung areas.

The mean radiation dose to the area of the lung where the tumor had developed in the case patients was 7.2 Gy among irradiated patients with lung cancer compared with 6.7 Gy among irradiated control subjects. The risk of lung cancer was found to increase significantly over categories of radiation dose (*P* for trend = .01) with an RR of 9.6 (95% CI = 0.93-98) for patients who received 9 Gy or more, as compared with those patients who received less than 1 Gy (Table 2). Too few patients had exposures greater than 9 Gy to reliably estimate the risk for a high-dose subgroup. It was striking, however, that, within the highest radiation dose category (>=9 Gy), the average radiation dose received by control subjects was much higher than that received by lung cancer case patients (21.0 versus 15.2 Gy). When dichotomizing the radiation dose category of 9 Gy or more at

Table 2. Relative risk (RR) of lung cancer in Hodgkin's disease patients stratified according to treatment and smoking

	No. of case patients	No. of control subjects	Crude RR (95% confidence interval)	P *	Adjusted RR (95% confidence interval)†	P ‡
Treatment						
Chemotherapy only	1	10	1.0		1.0	
Radiotherapy and chemotherapy	14	42	3.6 (0.41-32)	.25	2.7 (0.29-26)	.38
Radiotherapy only	15	30	5.3 (0.57-49)	.14	4.3 (0.44-43)	.21
Radiation dose to affected lung area, Gy						
<1, or no radiotherapy	2	17	1.0		1.0	
1-5	9	30	3.5 (0.39-32)	.26	2.9 (0.32-26)	.34
5-9	13	26	7.1 (0.81-62)	.08	6.3 (0.71-56)	.10
≥9	6	9	9.6 (0.93-98)	.06	8.9 (0.86-91)	.07
Linear trend test P value§				.01		.02
No. of cycles with alkylating chemotherapy						
0 or no chemotherapy	20	45	1.0		1.0	
1-6	6	19	0.74 (0.22-2.4)	.62	0.83 (0.23-3.1)	.79
>6	4	18	0.51 (0.15-1.7)	.28	0.74 (0.18-3.1)	.68
Mechlorethamine dose (cumulative), mg						
None	18	43	1.0		1.0	
≤115	6	21	0.75 (0.26-2.2)	.61	0.74 (0.23-2.4)	.62
>115	6	18	0.82 (0.28-2.4)	.73	1.32 (0.36-4.8)	.68
Linear trend per milligram			0.996 (0.990-1.003)	.25	0.998 (0.991-1.005)	.55
Procarbazine dose (cumulative), g						
None	18	39	1.0		1.0	
≤10.8	6	22	0.59 (0.19-1.8)	.36	0.80 (0.24-2.7)	.72
>10.8	6	21	0.63 (0.21-1.9)	.41	0.86 (0.25-2.9)	.81
Linear trend per gram			0.962 (0.908-1.019)	.18	0.974 (0.919-1.033)	.39
Total amount ever smoked, linear trend, per pack-year			1.017 (0.995-1.041)	.13	1.016 (0.992-1.041)	.19
Amount of smoking after diagnosis of Hodgkin's disease, pack-years‖						
0 or <1	8	43	1.0		1.0	
1-10	16	32	3.0 (1.1-8.0)	.03	2.9 (1.1-8.0)	.04
>10	6	6	7.0 (1.5-33)	.01	6.2 (1.2-3.1)	.03
Linear trend per pack-year			1.157 (1.030-1.298)	.01	1.141 (1.019-1.277)	.02
No. of packs per week at diagnosis of Hodgkin's disease‖						
0 or <1	6	27	1.0		1.0	
1-7	18	40	2.2 (0.72-6.9)	.17	0.6 (0.10-3.9)	.60
>7	6	14	2.0 (0.55-7.5)	.29	0.3 (0.04-3.0)	.33
No. of years since last smoking						
>10 or never smoked‖	3	22	1.0		1.0	
1-10	7	18	2.9 (0.67-13)	.15	2.3 (0.46-12)	.30
<1	20	41	3.5 (0.94-13)	.06	1.2 (0.20-6.8)	.87

* P value for crude RR.

† Treatment, radiation dose: adjusted for amount of smoking after diagnosis of Hodgkin's disease (categorical variable). Number of cycles with chemotherapy, mechlorethamine dose, procarbazine dose, number of packs per week at diagnosis of Hodgkin's disease, and number of years since last smoking: adjusted for amount of smoking after diagnosis of Hodgkin's disease (categorical variable) and adjusted for log-transformed radiation dose to the lung. Total amount ever smoked and amount of smoking after diagnosis of Hodgkin's disease adjusted for log-transformed radiation dose.

‡ P value for adjusted RR.

§ P value for linear trend test across categories.

‖ All smoking data were missing for one control subject.

the median dose (16 Gy), we found an increased risk of 14-fold (95% CI = 1.2-164) for subjects exposed to 9-15 Gy (based on four case subjects and four control subjects) and a 5.7-fold increased risk (95% CI = 0.39-83) for subjects exposed to 16 Gy or more (based on two case patients and five control subjects), suggesting a possible downturn in risk for exposures greater than 9 Gy. The effect of radiation dose as a continuous variable was best fitted by including the log-transformed dose into the model (*P* for trend = .07). Adjustment for smoking history and chemotherapy did not alter much (less than 5% change) the risk estimates for radiation dose. The number of episodes of radiation treatment was not associated with risk of lung cancer (more than one episode versus one episode: RR = 1.2; 95% CI = 0.33-4.4).

The number of cycles with alkylating chemotherapy was not associated with risk of lung cancer (Table 2). Adjustment for radiation dose resulted in slightly greater RRs (although still below 1.0) because patients treated with chemotherapy had received radiotherapy less frequently than patients not treated with chemotherapy. The type of chemotherapy used most extensively was treatment with mechlorethamine–procarbazine combinations. Overall, 40% of lung cancer case patients (versus

48% of the control patients) had been treated with combinations of this type. Neither the cumulative dose of mechlorethamine nor the cumulative dose of procarbazine was significantly related to the risk of lung cancer. The inclusion of the cumulative doses of mechlorethamine and procarbazine as continuous variables in the logistic regression model produced *P* values for linear trend of .55 and .39, respectively (adjusted for radiation dose and smoking; Table 2). Too few patients received other possibly carcinogenic agents to estimate dose relationships for these drugs. The number of case patients and control subjects who ever used the agents cyclophosphamide (four case patients and 13 control subjects), lomustine (no case patients and six control subjects), and bleomycin (no case patients and five control subjects) was not suggestive of any association with the risk of lung cancer. The only striking observation was that two lung cancer case patients and only one control subject had been treated with teniposide (RR = 11.3; 95% CI = 0.93-138).

As was expected, the total amount ever smoked, as expressed in pack-years, was associated with lung cancer risk, although not significantly *(P* = .13). Relationships with lung cancer risk in the expected direction were also found for the number of cigarettes smoked at diagnosis of Hodgkin's disease and the number of years since last smoking (Table 2). The smoking variable that showed the strongest relation to lung cancer risk was the number of pack-years smoked after diagnosis of Hodgkin's disease. Patients who smoked more than 10 pack-years after Hodgkin's disease diagnosis were subject to a sixfold elevated risk of lung cancer compared with patients who smoked less than 1 pack-year *(P* = .03; adjusted estimate for radiation dose). In addition, the test for linear trend of increasing lung cancer risk with increasing number of pack-years smoked after Hodgkin's disease diagnosis was significant at the .02 level. Further adjustment for other smoking variables (e.g., pack-years smoked before Hodgkin's disease diagnosis or number of years since last smoking) yielded similar RR estimates.

The modifying effect of smoking on the risk due to radiotherapy was first evaluated by fitting radiation dose–response slopes simultaneously for subjects who had smoked after diagnosis of Hodgkin's disease and for those who had not. For patients who had smoked 1 or more pack-years after diagnosis of Hodgkin's disease, the risk of lung cancer increased significantly with increasing (log-transformed) radiation dose *(P* = .027), whereas no such trend was observed among patients who had smoked less. The difference in dose–response trends between these two smoking categories was statistically significant *(P* = .04). When only two exposure categories of radiation dose were distinguished (<4 Gy and >=4 Gy), patients who had smoked 1 or more pack-years following Hodgkin's disease diagnosis and who were in the high-radiation-dose category had a 20-fold increased risk of developing lung cancer compared with smokers in the low-radiation dose category *(P* = .009). In contrast, no elevated risk for the higher dose category was observed in patients who had smoked less than 1 pack-year after Hodgkin's disease diagnosis (RR = 0.31; 95% CI = 0.05-1.8). When radiation dose was grouped into three exposure categories, the conditional logistic model used for the matched analysis did not attain convergence because of small numbers. Therefore, Table 3 shows the results of an unmatched logistic model in which, for smokers and nonsmokers separately, RRs were estimated according to three levels of radiation dose. Again, in subjects who continued smoking following Hodgkin's disease diagnosis, there was a significant increase in lung cancer risk over categories of radiation dose, while hardly any increase due to radiation was noted among Hodgkin's disease patients who smoked less than 1 pack-year after the diagnosis had been made.

Table 3. Risk of lung cancer according to amount of smoking after diagnosis of Hodgkin's disease and radiation dose to affected lung area

	Unmatched relative risks* (95% confidence interval): amount of smoking†	
Radiation dose, Gy	0 or <1 pack-year	≥1 pack-years
<1‡	1.0 (one case/five controls)	0.48 (0.02-10.1) (one case/12 controls)
1-5	0.99 (0.07-14.7) (two cases/19 controls)	7.7 (0.58-102) (seven cases/10 controls)
≥5	2.5 (0.21-29.4) (five cases/19 controls)	9.1 (0.78-106) (14 cases/16 controls)
	P for trend = .43	*P* for trend = .01

* Adjusted for all matching variables.

† Table excludes one control subject for whom amount of smoking could not be determined.

‡ The case/control subjects who received no radiation in this category are as follows: For 0 or <1 pack-year, one case and five controls, for >=1 pack-year, zero cases and five controls.

Finally, the effects of the matching variables (age at diagnosis of Hodgkin's disease and time since Hodgkin's disease diagnosis) on the risk estimates were considered in a stratified analysis. The RR of lung cancer associated with radiotherapy was higher in patients diagnosed with Hodgkin's disease below the median age of 50 years than among patients diagnosed at an older age. Furthermore, the risk related to radiotherapy increased with time since Hodgkin's disease diagnosis. In contrast, the modifying effect of smoking tended to be stronger in the older age group and in patients with a relatively short time since Hodgkin's disease diagnosis (<7 years). Possibly because of the small numbers of subjects available for subgroup analyses, none of these differences reached statistical significance.

Discussion

To our knowledge, our study is the first to reliably examine the modifying effect of smoking on the relationship between therapeutic irradiation and lung cancer risk. On the basis of nearly complete smoking histories and individually estimated radiation doses to affected lung areas, we found that lung cancer risk rose with increasing radiation dose. Positive interaction on a multiplicative scale was present between the carcinogenic effects of smoking and radiation. In patients who smoked after diagnosis of Hodgkin's disease, the increase in lung cancer risk with radiation dose was significantly greater than among patients who refrained from smoking. Extensive data on the doses of all cytostatic agents received were available in our study, but no association between lung cancer risk and any type of chemotherapy was found.

The joint effects of smoking and radiation have been examined in two other settings. Studies in uranium miners exposed to radon have indicated that smoking and radiation may act multiplicatively (or at least supra-additively) in the causation of lung cancer *(10)*. This finding would imply that the absolute risk of developing radon-induced cancer is much higher in smokers than in nonsmokers *(10,16-18)*. The data for atomic bomb survivors are equally compatible with a multiplicative and an additive model *(10,19)*, while in our own study the combined effects of smoking and radiotherapy for Hodgkin's disease are significantly stronger than multiplicative. When evaluating the joint effects of radiation exposure and smoking, it is important to consider the characteristics of the three study populations and their exposure situations. Differences in radiation type and energy, duration, and fractionation of exposure, as well as volume of lung irradiated, may account for the different risk models presented for the combined effects of irradiation and smoking. Also, the sequencing of radiation and smoking may explain part of the differences between the studies *(see below)*. Furthermore, it must be kept in mind that, in nearly all studies of the joint effects of smoking and radiation, the number of lung cancer patients was small, and the differences in goodness of fit between the various models were often marginal. Thus, chance may have played a role in the favoring of a specific model.

It is striking to note that the number of pack-years smoked after diagnosis of Hodgkin's disease was the smoking variable most strongly related to lung cancer risk in our study. Although the amount smoked after Hodgkin's disease constituted only, on average, 20% of the total number of pack-years smoked, the number of years smoked before diagnosis of Hodgkin's disease was not a significant factor in a model accounting for amount smoked after diagnosis. Furthermore, positive interaction on a multiplicative scale was present only between radiotherapy and amount of smoking after Hodgkin's disease diagnosis and was not present—or present to a much lesser degree—for other smoking variables, such as amount smoked at diagnosis of Hodgkin's disease or total amount ever smoked. It would have been interesting to examine the effect of smoking during estimate of relevant dose. To obtain the most accurate dose–response data, the radiation dose to the lung should ideally be estimated to the precise site within the lung where the tumor developed. Such measurement proved not to be feasible in our study; the large size of most tumors precluded any classification more precise than one based on lobes and bronchi of origin. Thus, assuming that radiation dose has been misclassified to some extent, it is possible that the strength of the radiation–lung cancer association has been underestimated in our study as well as in other studies. A tentative conclusion on the basis of present evidence would then be that lung cancer risk rises with increasing dose up to 9-10 Gy, above which the dose–response relationship is not yet clear. More studies are needed to evaluate the radiation–lung cancer association, especially in the high-dose ranges of therapeutic irradiation.

Two studies *(5,13)* found evidence of increased lung cancer risk in Hodgkin's disease patients treated with chemotherapy, while two other studies *(4,6)* found no such increase in risk. No association with any type of chemotherapy or with the cumulative doses of commonly used cytostatic agents emerged from our case–control study. In fact, the RRs associated with number of cycles and cumulative doses of mechlorethamine and procarbazine were slightly less than unity. Information on names and doses of cytostatic agents was very complete in our study, and all RRs were adjusted for the possible confounding effects of radiotherapy and smoking, using accurate data on radiation dose. Furthermore, cases and controls were sampled from a cohort with comparable or even longer follow-up than in the two positive studies *(5,13);* and it is reassuring that an overall effect of the use of chemotherapy on lung cancer risk has also not been found in the cohort (one case observed versus 0.89 expected) *(4)*. Thus, it seems very unlikely that we have missed a real association.

Several cytostatic agents, such as mechlorethamine and chlorambucil, have been shown to induce lung tumors in experimental animals *(30)*. Thus, further case–control studies with a higher percentage of lung cancer cases 10-20 years after treatment are certainly warranted to examine whether chemotherapy on its own or in combination with radiotherapy exerts a carcinogenic effect in patients with Hodgkin's disease.

The average age at diagnosis of Hodgkin's disease in our

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Notes

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